Advances in endoscopic resection and radiofrequency ablation of early esophageal neoplasia
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Introduction and outline
INTRODUCTION

Barrett’s esophagus is the most important known risk factor for esophageal adenocarcinoma. Esophageal adenocarcinoma is the dominant type of esophageal cancer in the western world, whereas in Asia squamous cell carcinoma is the most frequent esophageal cancer. In Barrett’s esophagus, the normal whitish colored squamous epithelium of the esophagus has been replaced by salmon-colored columnar epithelium, which is characterized histologically by the presence of goblet cells. Barrett’s esophagus (BE) was named after the surgeon Norman Barrett, who described this condition in 1950. Later, it was discovered that BE was an acquired premalignant condition resulting from long-standing gastro-esophageal reflux. To detect high-grade dysplasia or carcinoma at an early stage, Barrett’s patients are entered into surveillance programs, with endoscopic inspection and biopsies of the Barrett’s segment every 1-3 years. Until recently, patients with high-grade dysplasia or early carcinoma (early neoplasia) of their BE underwent surgical esophagectomy. Today, endoscopic treatment is the first choice treatment for these patients, which is a safe and effective, less invasive alternative to surgery. The technique of endoscopic resection (ER) was developed by the Japanese endoscopist H. Inoue in 1989. He was the first to endoscopically remove early neoplastic gastric and squamous esophageal lesions using a transparent cap and a coagulation snare. Since then, the technique of ER in the esophagus has been adopted by endoscopists in Europe, mostly for the treatment of early neoplasia in Barrett’s esophagus. However, after focal ER as a monotherapy, the remaining Barrett’s epithelium is still at risk for malignant progression. In the past decade therefore the paradigm shifted from focal ER of lesions to complete removal of the Barrett’s epithelium using ablation and endoscopic resection techniques.

In the past ten years, our research group has studied the safety and efficacy of several endoscopic treatment techniques for early neoplasia in the upper gastrointestinal tract. In 2000, endoscopic resection was used in Barrett’s esophagus patients as a mono-therapy to remove visible lesions containing early neoplasia. Although endoscopic resection was found to be safe and effective, the risk for metachronous lesions after focal ER was approximately 30%. Therefore, in subsequent treatment protocols we shifted from focal treatment of the visible lesion to endoscopic removal of the complete Barrett’s segment. For the removal of the residual Barrett’s epithelium after ER, we initially used ablation with photodynamic therapy using 5-aminovulnic acid as photosensitizer. The results of this combined approach were however disappointing: the majority of patients had residual BE after treatment and only a minority of patients (27%) showed sustained remission of early neoplasia. Therefore, in 2003, we moved to stepwise radical endoscopic resection (SRER). Our studies showed that SRER is a safe and effective treatment modality for the removal of the complete BE segment in several ER sessions. However, the SRER technique proved to be technically demanding and stenosis occurred frequently. In this period, we developed a training program in ER for endoscopists to implement endoscopic resection in a number of selected centers in the Netherlands. Anticipating that a growing number of patients with early Barrett’s neoplasia would require treatment, we aimed at increasing the capacity and quality of ER treatment in our country.
In 2005, a new promising treatment modality became available: radiofrequency ablation (RFA) using the HALO system. We were the first center worldwide to study the safety and efficacy of RFA in BE patients with high-grade dysplasia and to combine ER and RFA for lesions containing high-grade dysplasia or early cancer. The results of the first 23 patients were excellent with 100% eradication of early neoplasia and Barrett’s epithelium, and complications were rare and mild. We subsequently studied the combined approach of ER for focal lesions followed by RFA for the remaining Barrett’s epithelium in a European multicenter setting. Because of the favorable initial results of RFA treatment and our good experiences with SRER, we conducted a randomized trial to compare SRER with combined ER followed by RFA. In the meantime, large prospective trials in the USA confirmed the excellent safety and efficacy of RFA for non-dysplastic and dysplastic Barrett’s esophagus. To improve the practicality of the RFA treatment procedure, we designed studies aiming at easier and faster focal and circumferential RFA. Also, we studied the feasibility of newer indications for the combined use of ER and RFA such as early squamous neoplasia of the esophagus, and patients with Barrett’s neoplasia with widespread non-flat lesions, that were treated with RFA and ER in a the same endoscopic treatment session.
OUTLINE OF THE THESIS

Part One: Endoscopic Resection
In the first part the focus is on endoscopic resection of early esophageal neoplasia. In Chapter 1 we assessed the outcomes of the first 120 patients treated with ER within the setting of the ER training program in the Netherlands, to gain insight into the learning curve of the ER procedure. In Chapter 2 we studied the most frequently encountered technical difficulties during the ER procedure experienced by the endoscopists and the teachers of this training program. In Chapter 3 we compared the safety and efficacy of two different ER techniques, the ER-cap technique and the multiband mucosectomy technique, in a randomized trial.

Part Two: Radiofrequency ablation
This part of the thesis contains several studies on radiofrequency ablation of early esophageal neoplasia, starting with a technical review of the RFA technique in Chapter 4. In Chapter 5 we report on a randomized trial that compared the safety and efficacy of SRER versus the combined approach of ER followed by RFA. This study was performed in a European multicenter setting for patients with early neoplasia in their Barrett’s segment with a maximal length of 5 cm. In Chapter 6 we studied the safety and efficacy of RFA for patients with longer Barrett’s segments in a series of patients with early neoplasia in their Barrett’s esophagus with a minimal length of 10 cm. In Chapter 7 we evaluated the feasibility of RFA for early neoplasia of the squamous esophagus with or without prior ER in 13 patients. Chapter 8 and 9 contain two multicenter randomized trials in which we aimed to simplify the RFA procedures for circumferential and focal RFA respectively, by making the regimen easier and faster, while maintaining safety and efficacy. In Chapter 8 we compared three different ablation regimes for circumferential RFA using the HALO360-electrode. In Chapter 9 two different focal ablation regimes using the HALO90-electrode were compared. To gain insight into which patients have a poor response to RFA treatment, we assessed the characteristics of 278 patients treated with RFA in a European multicenter setting, and related potential predictive markers to the response at three months after circumferential balloon-based RFA, as described in Chapter 10.

Part Three: Single Session RFA and ER
Whereas in current treatment protocols ER is followed by RFA treatment after 6-8 weeks allowing for healing of the ER wound, in the ‘single session’ approach of combined RFA and ER, we performed RFA directly followed by ER of the visible lesion in the same treatment session. Chapter 11 contains an animal study to assess the feasibility of ER immediately followed by RFA and RFA immediately followed by ER. In Chapter 12 we describe the results of a series of 24 consecutive patients who were treated with single session ER and RFA for lesions in Barrett’s esophagus containing early neoplasia.